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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
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ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/800,333	HEKIMI ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,8 and 29-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,8 and 29-31* is/are rejected.

7)☒ Claim(s) *1,6 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/30/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Applicant's response of May 30, 2007, to the non-final action dated November 30, 2006 has been entered. Claims 1, 6, 8 and 29-31 are pending in the application. Claims 1, 6, 8 and 29-31 have been amended and claims 2-5, 7 and 9-28 cancelled. No claims were newly added. Claims 1, 6, 8 and 29-31 are currently under examination. Applicants should note that the claims have been examined commensurate with the scope of the elected invention, wherein the test *C. elegans* comprises, at least one mutation in the clk-1 gene, or at least one mutation in the clk-1 gene and at least one mutation in the dsc-4 gene.

New Claim Objections

Claims 1, 6 and 8 are newly objected to because of the following informalities: the claims have not been amended to recite the elected invention and the species of the invention. The instant claims have been amended to include non-elected subject matter, i.e. mutation in the disc-3 gene; and various non-elected phenotypes of the test *C. elegans*. Appropriate correction is required.

Response to Objections to the Specification

The disclosure was previously objected to in the office action dated November 30, 2006, as containing embedded hyperlinks and/or other form of browser-executable code. Applicants have amended the specification, delete said hyperlinks, obviating the ground for objection. Thus, the previous objection is hereby withdrawn.

Response to Failure to Comply with 37CFR §1.821-1.825

The disclosure of the application was objected to in the previous office action of November 30, 2006, as lacking SEQ ID NOS for the amino acid sequences recited in the sequence alignments of Figures 3A and 11A-F, as well as the amino acid Figure. In view of Applicants' amendment of the brief description of the drawings for Figures 3, 10 and 11 to refer to the sequences by appropriate SEQ ID NOS, the previous objection is hereby withdrawn.

Response to Claim Rejections - 35 USC § 112 – Written Description

Claims 1, 6-8 and 29-31 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Applicants' cancellation of claim 7 obviates its rejection. In view of Applicants' amendments of claims 1, 6, 8 and 31 directing the claims to the species of *C. elegans*, the previous rejection is hereby withdrawn.

Response to Claim Rejections - 35 USC § 112 - Lack of Enablement

Claims 1, 6-8 and 29-31 stand rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. Applicants' cancellation of claim 7 obviates its rejection. Applicants' amendment of the claims directing the claimed methods to the species of *C. elegans*, partly addresses the issues outstanding in the rejection. The rejection set forth on pp. 6-10 of the previous office action dated November 30, 2006 is maintained for claims 1, 6, 8 and 29-31 for reasons of record.

Applicants disagree with the rejection, arguing that the prior art of McKay et al. suggests that C. elegans is an appropriate model of lipid storage, and an art-accepted platform for discovering human genes that play a role in human metabolic diseases. Applicants state that although clk-1 mutations in C. elegans are not directly associated with human lipid/lipoprotein-related diseases, DSC-4 is the homolog of the large subunit of human microsomal triglyceride transfer protein (MTP) that is required for the synthesis of apolipoprotein B-containing lipoproteins, and that one of skill in the art would reasonably expect that inhibitors of MTP would inhibit dsc-4 and produce a phenotype similar to a dsc-4 mutation in C. elegans. Applicants' arguments have been fully considered, but are not found persuasive.

Regarding the use of *C. elegans*, the issue is not whether the nematode may be used as an experimental model to discover human genes, but whether mutations in the clk-1 and/or dsc-4 genes may be used to identify compounds that modulated lipid or lipoprotein metabolism in humans, based on the phenotypic screen relating to defecation cycle, as instantly claimed. McKay et al. are silent on mutations in the clk-1 and dsc-4 genes.

With regard to the proposed inhibitors of MTP having the ability to inhibit dsc-4, the specification describes the isolation of the dsc-4 gene (as "a suppressor of the slow defecation phenotype of clk-1 mutants") but further states that the dsc-4 mutation does not suppress all aspects of the clk-1 phenotype (p. 112). The specification additionally teaches that dsc-4 encodes a protein, which is similar in sequence to the large subunit of the microsomal triglyceride transfer protein, MTP, but that " The mutation sites of dsc-4 (qm182) were in the apo B-binding domain and were different from those found in abetalipoproteinemia patients." (p. 114). It is further noted that C. *elegans* cannot synthesize cholesterol (p. 119). Moreover, in experiments aimed at phenocopying dsc-4 mutations by cholesterol depletion of *C. elegans*, the specification states: "in general, the effect of cholesterol depletion was much more severe and included numerous defects not seen in dsc-4 mutants...One possibility is that dsc-4 polypeptide is not as stringently required for secretion of LDL-like lipoproteins in worms as is MTP in mammals. Another possibility is that there are other pathways of cholesterol redistribution from the intestine to peripheral tissues in worms" (p. 119). Taken together, the preceding observations suggest that to demonstrate a linkage between dsc-4 gene function and human cholesterol metabolism would require further experimentation.

Moreover, the compound screening method additionally requires a mutation in the clk-1 gene to provide the phenotype for a reversion screen. Applicants further state that the level of oxidation of LDL-like lipoproteins is decreased by the presence of demethoxyquinone (DMQ), a product produced in *C. elegans* as a result of a mutation in clk-1, and that a skilled person would recognize that a test compound can rescue partially or completely the clk-1 phenotype. Such is not found persuasive, because as the specification teaches, "[M]utations in the *Caenorhabditis elegans* gene clk-1 are highly pleiotropic, affecting the rates of physiological traits that occur over a wide range of timescales" (p. 1). Further, clk-1 encodes a mitochondrial protein that encodes a hydroxylase required for the biosynthesis of ubiquinone (UQ), a prenylated

benzoquinone lipid that functions as a transporter of electron complexes II and III in the respiratory chain (p. 2). "It is however, not clear how the absence of UQ relates to the other mutant phenotypes as there is no correlation between this biochemical phenotype and the severity of the overall phenotype." (p. 3). "The periodicity of the defecation cycle can be altered by mutations in at least 13 genes (Dec phenotype)." (p. 3). Therefore, in view of the absence of a nexus between clk-1 and dsc-4 mutations and cholesterol regulation in humans a person of ordinary skill in the art would have to engage in additional undue experimentation to establish a role between clk-1 mutation and cholesterol metabolism in humans and to determine whether any phenotypic reversion of the defecation cycle in a test *C. elegans* carrying a clk-1 mutation, in a compound screening assay, may be attributed to dsc-4 or one of the many other genes capable of rescuing the clk-1 phenotype.

Applicants argue that while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976). Accordingly, the use of the described phenotypes in a clk-1 mutant (without any additional dsc mutation) in screening for drug candidates useful for human lipid/lipoprotein- related diseases is enabled. Further stating that the enablement of the claimed invention does not require a direct functional correspondence of a mutation in a *C. elegans* gene with a mutation in a human gene that is associated with a human disease such as metabolic diseases that involve multiple genetic factors.

Such is not found persuasive, because it is unclear how a of clk-1 mutant (in the absence of additional dsc mutations) may be used as a test nematode in modulating lipid or lipoprotein levels, as the clk-1 product is not required for LDL-like lipoprotein secretion. Furthermore, having screened compounds in a *C. elegans* having only a clk-1 mutation, the person of skill in the art would not know whether the observation of a reverted phenotype would be related to modulation of a lipid or lipoprotein or the activation or inhibition of one of numerous gene products capable of rescuing the clk-1 phenotype, that are additionally not related to lipid metabolism. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue (*In re Angstadt*). Factors examined according to *In re Wands*, have been previously set forth on the record. A person of skill in the

art would therefore have to engage in additional undue experimentation to define conditions wherein test *C. elegans* may be produced that comprise mutations correlated with cholesterol abnormality in humans, and to further employ the test *C. elegans* as a model for screening compounds for treatment of cardiovascular, liver and intestinal disease in humans. Such further experimentation is regarded as undue and unpredictable, in view of the absence of sufficient guidance in either the instant specification or the prior art.

As previously stated, the specification and the prior art are silent on any association between clk-1 mutation and any disease in humans. It is further apparent from the foregoing that there is no clear nexus between clk-1 and dsc-4 mutations in C. *elegans* and cholesterol regulation in humans.

Therefore, the rejection of claims 1, 6-8 and 29-31 is maintained for reasons of record and the preceding discussion.

Response to Claim Rejections - 35 USC § 112- Second Paragraph

Claims 1, 6-8 and 29-31 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite, in the office action dated November 30, 2006. Applicants' cancellation of claim 7 obviates its rejection. In view of Applicants' amendments of claims 1 and 6, to recite that the test *C. elegans* comprises at least one mutation in the clk-1 gene, and including the active step of treating test *C. elegans* with a compound, obviating the grounds for rejection, the previous rejections are hereby withdrawn.

Conclusion

Claims 1, 6, 8 and 29-31 are not allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00-4:00 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on **(571) 272-2739**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199**.

Fereydoun G. Sajjadi, Ph.D.
Examiner, USPTO, AU 1633

/Joseph Woitach/
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